

# SCIENCE

Published by the **American Association for the Advancement of Science (AAAS)**, *Science* serves its readers as a forum for the presentation and discussion of important issues related to the advancement of science, including the presentation of minority or conflicting points of view, rather than by publishing only material on which a consensus has been reached. Accordingly, all articles published in *Science*—including editorials, news and comment, and book reviews—are signed and reflect the individual views of the authors and not official points of view adopted by the AAAS or the institutions with which the authors are affiliated.

The American Association for the Advancement of Science was founded in 1848 and incorporated in 1874. Its objectives are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve the effectiveness of science in the promotion of human welfare, to advance education in science, and to increase public understanding and appreciation of the importance and promise of the methods of science in human progress.

## Membership/Circulation

**Director:** Michael Spinella  
**Deputy Director:** Marlene Zendell  
**Member Services:** Rebecca Dickerson, *Manager*; Mary Curry, *Supervisor*; Pat Butler, Helen Williams, Laurie Baker, *Representatives*  
**Marketing:** Dee Valencia, *Manager*; Jane Pennington, *Europe Manager*; Hilary Baar, *Associate*; Angela Mumeka, *Coordinator*  
**Research:** Renuka Chander, *Manager*  
**Business and Finance:** Jacquelyn Roberts, *Manager*; Robert Smariga, *Assistant Manager*  
**Administrative Assistant:** Nina Araujo de Kobes  
**Science Member Services**  
 Marion, Ohio: 800-347-6969;  
 Washington, DC: 202-326-6417  
**Other AAAS Programs:** 202-326-6400

## Advertising and Finance

**Associate Publisher:** Beth Rosner  
**Advertising Sales Manager:** Susan A. Meredith  
**Recruitment Advertising Manager:** Janis Crowley  
**Advertising Business Manager:** Deborah Rivera-Wienhold  
**Finance:** Randy Yi, *Senior Analyst*; Shawn Williams, *Analyst*  
**Marketing:** John Meyers, *Manager*; Allison Pritchard, *Associate*  
**Traffic Manager:** Tina Turano  
**Recruitment:** Terri Seiter, *Assistant Manager*; Debbie Cummings, Celeste Wakefield, Rachael Wilson, *Sales*  
**Reprints Manager:** Corrine Harris  
**Permissions Manager:** Arlene Ennis  
**Sales Associate:** Carol Maddox

**PRODUCT ADVERTISING SALES: East Coast/E.**  
 Canada: Richard Teeling, 201-904-9774, FAX 201-904-9701 • **Southeast:** Mark Anderson, 305-856-8567, FAX 305-856-1056 • **Midwest:** Elizabeth Mosko, 312-665-1150, FAX 312-665-2129 • **West Coast/W. Canada:** Neil Boylan, 415-673-9265, FAX 415-673-9267 • **UK, Scandinavia, France, Italy, Belgium, Netherlands:** Andrew Davies, (44) 457-838-519, FAX (44) 457-838-898 • **Germany/Switzerland/Austria:** Tracey Peers, (44) 270-760-108, FAX (44) 270-759-597 • **Japan:** Mashu Yoshikawa, (3) 3235-5961, FAX (3) 3235-5852  
**RECRUITMENT ADVERTISING SALES: US:** 202-326-6555, FAX 202-682-0816 • **Europe:** Gordon Clark, (44) 0223-302067, FAX (44) 0223-302068 • **Australia/New Zealand:** Keith Sandell, (61) 02-922-2977, FAX (61) 02-922-1100  
 Send materials to *Science* Advertising, 1333 H Street, NW, Washington, DC 20005.

**Information for Contributors** appears on pages 37–39 of the 7 January 1994 issue. Editorial correspondence, including requests for permission to reprint and reprint orders, should be sent to 1333 H Street, NW, Washington, DC 20005.  
**Internet addresses:** science\_editors@aaas.org (for general editorial queries); science\_letters@aaas.org (for letters to the editor); science\_reviews@aaas.org (for returning manuscript reviews); membership@aaas.org (for member services); science\_classifieds@aaas.org (for submitting classified advertisements)

## On the Potential of Molecular Computing

In his report “Molecular computation of solutions to combinatorial problems” (11 Nov., p. 1021), Leonard M. Adleman describes a method for finding Hamiltonian paths in directed graphs that is based on molecular biological tools. This approach is demonstrated on a particular graph with seven vertices and 13 edges. Adleman and David K. Gifford, in his Perspective “On the path to computation with DNA” (p. 993), speculate on the possibility of performing difficult computational tasks by operating at the molecular level. We consider the applicability of this intriguing idea in light of the fact that the type of problem solved in the report, called an NP-hard problem, becomes exceedingly difficult as the size of the problem grows. It is known that sparse directed graphs (that is, graphs with few edges) almost surely have no Hamiltonian path, while, for graphs with many edges (dense graphs), almost surely one exists. On the basis of this fact from random graph theory, simple algorithms were designed for finding Hamiltonian paths in graphs that are either very sparse or very dense (1). Therefore, the power of any computational technique for this problem should be tested on “middle-ground” graphs, with  $n$  vertices and about  $n(\log n)$  edges. Step 1 in Adleman’s experiment calls for expanding all paths on  $n$  vertices—a total of  $(\log n)^n$  in this case. Each path consists of a  $(20n)$ -mer oligonucleotide. Therefore, such an experiment involves at least  $20 n (\log n)^n$  base pairs. If Adleman’s method is to be expanded one order of magnitude, to deal with graphs on 70 vertices, the total mass of nucleotides involved in the experiment would reach  $10^{25}$  kilograms (on the basis of the average molecular mass of a nucleotide). These quantities get much higher with any further increase in the number of edges.

Other inherent limitations further reduce the size,  $n$ , of graphs to which Adleman’s method is applicable: “Coupon-collector” bounds from statistics (2) should be observed so that every path type is generated in the random ligation step. Cost, labor, experimental errors, and reaction time further reduce this number. In

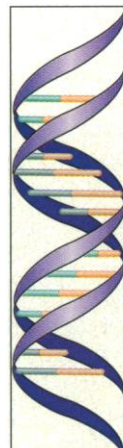


ILLUSTRATION: K. SUTLIFF

**DNA computing.**  
 Tracking the traveling salesman through molecular solutions.

fact, it seems impossible for graphs with more than 30 vertices to be handled by this approach.

Conventional state-of-the-art algorithmic techniques fare much better: The related, but even harder “traveling salesman” problem is currently solved for graphs on a few thousand vertices, the largest instance being a specific graph with 7397 vertices (3). These conventional computers perform so well because of the advanced algorithms they use. For the dream of a molecular biological computer to materialize, a much richer set of instructions than those employed by Adleman may have to be emulated.

**Michal Linial**

*Department of Biological Chemistry,  
 Hebrew University,  
 Jerusalem 91904, Israel*

**Nathan Linial**

*Institute of Computer Science,  
 Hebrew University,  
 Jerusalem 91904, Israel*

## References

1. B. Bollobas, *Random Graphs* (Academic Press, New York, 1985).
2. W. Feller, *An Introduction to Probability Theory and Its Applications* (Wiley, New York, 1968).
3. D. Applegate, B. Bixby, V. Chvátal, W. Cook, “Finding cuts in the TSP (a preliminary report)” (DIMACS Technical Report 95-05, Center for Discrete Mathematics and Theoretical Computer Science, New Brunswick, NJ, 1995).

Adleman proposes a new approach to computing using DNA molecules which may have implications for certain demanding computing applications. He uses the directed Hamiltonian path problem as an example and shows that it can be solved by using a combination of several well-known molecular biological techniques. This approach has enormous potential for further development. For example, Adleman’s system can be modified to find the shortest Hamiltonian cycle in a particular system and thus can be used to solve the well-known “traveling salesman” problem (1). This can be accomplished by encoding path length information using oligonucleotides of different lengths. After ligation and amplification by polymerase chain reaction (PCR), affinity purification can be applied directly to the PCR products. Gel electrophoresis will then reveal the shortest PCR product

that will represent the shortest Hamiltonian cycle. With the recent introduction of long-range PCR techniques (2) and mega-primer PCR (3), this approach can theoretically be used to solve very complex problems.

However, limitations of the method exist, the most important one being that the number of molecules required for the computation of complex problems rises exponentially as the complexity of the problem increases. For instance, for Hamiltonian problems with 23 vertices, kilogram quantities of each oligonucleotide will be needed to generate the required solution with reasonable probability. This will require unrealistic quantities of enzymes and will overload the capacity of the subsequent analytical step, such as agarose gel electrophoresis. These considerations imply that at least at present, molecular computing is likely to have no applicability for problems with an intermediate complexity. For simpler problems, conventional computing provides ease of operation, while for complex problems, molecular computing will be limited by the constraints imposed by the requirement of raw materials.

Finally, the comparison of energy efficiency calculated by Adleman does not take fully into consideration the enormous ener-

gy inefficiencies of many of the accompanying steps, such as thermal cycling for PCR, electrophoresis, and so forth. These energy premiums should be included in calculations before molecular computing can be used practically.

**Y.-M. D. Lo**

*Nuffield Department of Clinical Biochemistry,*

*John Radcliffe Hospital,*

*University of Oxford,*

*Oxford OX3 9DU, United Kingdom*

**K. F. C. Yiu**

*Oxford University Computing Laboratory,*

*Wolfson Building, Parks Road,*

*Oxford OX1 3QD, United Kingdom*

**S. L. Wong**

*Clarendon Laboratory, Parks Road,*

*Oxford OX1 3PU, United Kingdom*

#### References

1. C. H. Papadimitriou and K. Steiglitz, *Combinatorial Optimization: Algorithms and Complexity* (Prentice-Hall, Englewood Cliffs, NJ, 1982).
2. S. Cheng, S. Y. Chang, P. Gravitt, R. Respass, *Nature* **369**, 684 (1994).
3. G. Sarkar and S. S. Sommer, *BioTechniques* **8**, 404 (1990).

Adleman's report and the accompanying Perspective by Gifford on biomolecular computing are overly optimistic to a de-

gree that deserves comment. The novel technology of exhaustive search using a combinatorial oligonucleotide library subject to parallel selection and PCR amplification is applied to a hypothetical small problem, identification of a directed Hamiltonian path on a graph with seven nodes. The inferred capability of the technology to handle real-world problems when further developed requires an extrapolation that ignores the "combinatorial catastrophe" that is what makes NP-complete problems really hard. These difficulties are revealed by the following order-of-magnitude calculations.

The size of a combinatorial library implemented on a lab bench is limited by thermodynamics to something like Avogadro's number ( $\sim 10^{24}$ ). This is also the number of unique oligonucleotides of length 40 ( $4^{40} = 2^{80} = 10^{24}$ ). Adleman's representation of the seven-node problem already uses oligonucleotides of about this length. Clever coding might reduce the length of the representation, but one base per node is probably an unachievable lower limit. Real-world graphs for which directed Hamiltonian paths are required currently have hundreds to thousands of nodes-branches. Approximate Hamiltonian paths can be routinely obtained for

Leading supplier  
of life science research  
equipment to Uppsala  
(And the rest of the world)





such graphs. Representing these paths with a single base per node would require oligonucleotides with  $10^2$  to  $10^3$  bases. An exhaustive combinatorial library would involve  $4^{10^2}$  to  $4^{10^3}$  oligonucleotides, and  $4^{10^2}$  is  $10^{70}$  in very round numbers. This number is exceedingly large. By comparison, a crude estimate of the number of particles in the universe is  $10^{80}$ . Problems of this size are clearly beyond any imaginable improvement of the technology described by Adleman.

The problem of finding a directed Hamiltonian path in a graph is hard in the sense of computer science, being NP-complete. In another sense, however, it is easy because it can be solved without looking at every potential solution individually and deciding whether to accept or reject it. Let us call problems where every potential solution must be checked "truly hard." Biomolecular computing is likely to be more effective on truly hard problems, because the thermodynamically massive parallelism that it offers is not wasted on potential solutions that would not otherwise have had to be examined.

An example of a truly hard problem is to design an oligonucleotide of length  $L$  that binds with nanomolar affinity to some substance (A), with greater than  $10^4$

discrimination of a number of chemically similar substances (B, C, ...). Let  $L$  be about 20. This design is equivalent to solving a constrained nonlinear optimization problem with the objective function given by the interaction potential between the oligonucleotide and A, and with the constraints given by the interaction potentials between the oligonucleotide and B, C, ... . This optimization takes place in a space of dimension  $4^{20} \times 3^{20}$ , where the first term is the number of sequences and the second term is the number of configurations, assuming three rotamers for each oligonucleotide. Optimization in a space of dimension  $10^{20}$  is a very hard problem (not currently solvable on computers). For the chemical design problem, we currently have no idea how to proceed from first principles, so that we would have to look at every sequence in every configuration. The method of affinity selection and PCR amplification is yielding products in this area.

**Barry Bunow**

Civilized Software, Inc.,  
7735 Old Georgetown Road, Suite 410,  
Bethesda, MD 20814, USA

#### Notes

1. I thank Gary Knott for his help.

*Response:* Molecular computation is embryonic and will require considerable exploration before its potential and limitations are brought into clear focus. Certainly, as pointed out in the letters of M. and N. Linial and Lo, Yiu, and Wong, molecular computation is not ready to compete with electronic computation at this time.

Will it ever compete? That is an open question. An affirmative answer may require meeting numerous challenges:

- in biology and chemistry: challenges in understanding cellular and molecular mechanisms and making them available for use as 'primitives' in molecular algorithms.

- in computer science and mathematics: challenges in finding appropriate problems and efficient molecular algorithms to solve them.

- in physics and engineering: challenges in building large-scale, reliable molecular computers.

Happily, in the few months since my report appeared, there has been encouraging progress. Richard Lipton of Princeton University (this issue, p. 542) (1) has demonstrated that the famous "satisfiability" problem may be particularly amenable to the molecular methods that have thus far been elucidated. I have fol-

Uppsala (pronounced OOP-SA-LA) is a university town about 45 minutes by car from Stockholm, Sweden. The university here was founded in 1477 and has a lengthy tradition of developing exceptional life science researchers. (The great Carl von Linné and Anders Celsius both lived and worked in Uppsala.)

Pharmacia Biotech helped enlarge Uppsala's scientific scope by making it our home base. We settled here because when you're committed to being one of the world's leading suppliers of life science research products, equipment and methodologies, it helps to be at the source of bright young life scientists.

That Pharmacia Biotech hails from Sweden doesn't make us better – it just makes us Swedish. For many, that's

enough to remember us by. But if you would rather, Pharmacia Biotech is an international company committed to supplying life science researchers with the most advanced solutions available. Full-service offices on every continent and in over 27 countries mean that every minute of the day someone in the world is calling a Pharmacia Biotech office to ask us for advice on separating biomolecules or to enquire about our comprehensive range of products for molecular biology. (See why it's easier just to remember us as being Swedish.)

We realize it takes time to gauge a company's merits. So if you would like to learn more about Pharmacia Biotech, just call us at +46-18-16 50 00 and we'll send you a free copy of our company brochure. In Swedish, if you insist.



Uppsala, Sweden. (And the rest of the world)

Circle No. 21 on Readers' Service Card

lowed Lipton with the description of a hypothetical molecular computer which, if constructable, would solve hard instances of the satisfiability problem substantially faster than the fastest current super computer (2).

But it is too early for either great optimism or pessimism. Today's electronic computers are marvels of speed and efficiency. They are the product of a half century of extraordinary development. Molecular computers are less than a year old. Perhaps they will mature well—perhaps not.

In any case, molecular computers can contribute to our understanding of the nature of computation. They can cause us to revisit the question of what a computer is. In the end computers are simply physical devices obeying physical laws. Devices become "computers" when we learn to interpret their behavior appropriately. Molecular computers make it clear that such an interpretation can be imposed on devices very different from those to which we have grown accustomed. What other devices will become "computers" in the future?

Building a practical molecular computer is an exciting prospect, but it is not the only goal. We should not lose sight of the

fact that the primary reason for research in this area is to elucidate fundamental aspects of computation and biology. In this regard there is reason for optimism.

**Leonard M. Adleman**

Department of Computer Science, and  
Institute for Molecular Medicine  
and Technology,  
University of Southern California,  
941 West 37th Place,  
Los Angeles, CA 90089, USA  
E-mail: [adleman@cs.usc.edu](mailto:adleman@cs.usc.edu)

#### References

1. R. Lipton, *Science* **268**, 542 (1995).
2. L. Adleman, "On constructing a molecular computer, Draft," 11 January 1994 (by anonymous ftp: /pub/csinfo/papers/adleman/molecular\_computer.ps on usc.edu).



#### Gravitational Theory

Faye Flam's Research News article "Theorists make a bid to eliminate black holes" (23 Dec., p. 1945) could not have appeared at a more opportune time. Within weeks of its publication, astronomers announced two important findings. One is evidence for a supermassive object with

mass of 36 million suns that is a candidate for a black hole (1). The other is the nonexistence in Hubble Space Telescope images of material supposed to surround quasars, characterized by John Bahcall as "a giant leap backwards in our understanding of quasars" (2).

In the theory we advocate (3, 4), a large amount of matter can collapse, but does not form an event horizon. Radially directed light can always escape, although the red shift is great. The concept of horizon in Einstein's theory is misleading. Einstein's theory actually gives two spherically symmetric, nonisotropic solutions, one of which is the standard Schwarzschild metric. The other does not have an event horizon (4). These two solutions are structurally the same as the slab solutions in general relativity, where the unphysical features are attributed to "peculiar matter" (5). If one says the slabs are "peculiar matter," one also has to say that mass in the Schwarzschild solution is "peculiar matter." The theory we advocate gives a unique solution that corresponds to normal matter without any unphysical features. This solution does not have an event horizon, nor does it exhibit a curvature singularity at the origin. We urge the astronomical community

# Thermalase Tbr™ Thermostable DNA Polymerase



- Higher fidelity than Taq DNA polymerase
- Higher thermostability than Taq polymerase
- Long (6kb) primer extensions routinely achieved
- Economically priced

AMRESCO is proud to announce the addition of Thermalase Tbr™ Thermostable DNA Polymerase to

its offering of enzymes and reagents for molecular biology. Isolated from a proprietary strain of *Thermus brokianus*, Thermalase Tbr offers some distinct advantages over Taq polymerase in primer extension reactions.

AUSTRALIA: +61-2-5402055 AUSTRIA: +43-1-889-18-19 CANADA: +416-470-2520 CHINA: +852-8983008  
CZECH REPUBLIC: +42-5-740-938 FRANCE: +33-70-03-88-55 GERMANY: +49-51-50-686-0  
GREECE: +30-1-723523 HONG KONG: +852-8983008 HUNGARY: +42-5-740-938  
INDIA: +91-11-60-8710 IRELAND: +353-1-391212 ISRAEL: +972-2-520279  
ITALY: +39-2-5097-221 JAPAN: +81-3-3643-3271 KOREA: +82-2-203-0707  
MALAYSIA: +65-288-6388 MEXICO: +52-5-654-4245 NETHERLANDS: +31-75-31-05-53  
PANAMA: +507-26-0948 POLAND: +42-5-740-938 SINGAPORE: +65-288-6388  
S. AFRICA: +27-11-886-1900 SPAIN: +34-1-551-14-91 SWEDEN: +46-31-36-3000  
SWITZERLAND: +41-21-728-77-72 TAIWAN: +886-2-381-0844  
THAILAND: +66-2-2748331-3 U.K.: +44-622-678872  
VENEZUELA: +58-2574-8434 YUGOSLAVIA: +41-21-728-30-66

**NOW available  
in recombinant form**

Circle No. 30 on Readers' Service Card

**AMRESCO®**

AMRESCO Inc.  
30175 Solon Industrial Pkwy. • Solon, OH 44139  
(800) 829-2805 • FAX: (216) 271-1182

©1994 by AMRESCO Inc. All rights reserved. AMRESCO® is a registered trademark of AMRESCO Inc. 4/94